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Implementation of the Advanced Therapies Regulation: public consultation on the revision of Annex I to Directive 2001/83/EC - Public Consultation Paper Nr. 2008-04-08

Kommentare des Paul-Ehrlich-Instituts

Anlagen: 2

Sehr geehrte Damen und Herren,

vielen Dank für die Möglichkeit der Stellungnahme im Rahmen der o.g. Konsultation. Die folgenden Kommentare des Paul-Ehrlich-Instituts werden vom Bundesministerium für Gesundheit mitgetragen und nachdrücklich unterstützt.

Der Vorschlag der Europäischen Kommission zur Ergänzung des Anhang I der Richtlinie 2001/83/EG hinsichtlich der Arzneimittel für neuartige Therapien wird grundsätzlich begrüßt. Dies gilt auch für die vorgesehene Möglichkeit, bei der Entwicklung der Arzneimittel die Auswahl bestimmter Prüfmethoden auf der Grundlage einer Risikoanalyse zu treffen. Dieser bei biologischen Arzneimitteln grundsätzlich sachgerechte Ansatz ist jedoch im Lichte der generellen Anforderung der bestehenden einschlägigen Leitlinien zu sehen und darf nicht zum Wegfall von für die Bewertung des Arzneimittels erforderlichen Daten führen. Vorschläge zur Modifzierung des Anhang I der Richtlinie wurden in einer Tabelle zusammengefasst (Anlage 1).

Durch den Verweis in Artikel 2 Abs. 1a der Verordnung (EG) Nr. 1394/2007 hinsichtlich der Begriffsbestimmungen der Gentherapeutika und der somatischen Zelltherapeutika auf den Anhang I, Teil IV der Richtlinie 2001/83/EG kommt den Definitionen dieser Arzneimittel im Anhang I besondere Bedeutung zu.

Die von der Kommission vorgeschlagenen Definitionen sind deshalb bereits in den Fachkreisen eingehend diskutiert worden. Dabei ist deutlich geworden, dass die Definition der Gentherapie-Arzneimittel einerseits zu eng erscheint, weil Arzneimittel, die allgemein als Gentherapeutika begriffen werden und für die auch die spezifischen Anforderungen an die Herstellung und Prüfung von Gentherapeutika gelten müssen, nicht erfasst sind, andererseits aber auch eine deutlichere Abgrenzung wünschenswert ist.

Dies gilt insbesondere hinsichtlich der prophylaktischen Impfstoffe. Letztere werden, wenn sie aus dem Gebiet der Arzneimittel für neuartige Therapien stammen, auch gern als genetische Impfstoffe

gegen Infektionskrankheiten bezeichnet. Eine ausschließliche Einordnung von genetischen Impfstoffen für die Prophylaxe von Infektionskrankheiten in die Definition der Gentherapie-Arzneimittel sollte diskutiert werden, weil für diese Arzneimittelgruppe die etablierten Anforderungen für Impfstoffe nicht außer acht gelassen werden dürfen. Andererseits müssen jedoch alle wegen der biologischen Eigenart und Herstellungsweise solcher Impfstoffe erforderlichen spezifischen Anforderungen aus dem Bereich der Arzneimittel für neuartige Therapien gerade auch für genetische Impfstoffe gelten,.

Auch für menschliche somatische Zellen, die durch einen Gentransfer beispielsweise zu sog. „induced pluripotent stem cells“ geworden sind, sollten die Anforderungen des Teil IV gelten, auch wenn die beabsichtigte Wirkung der ausgehend von diesen Zellen entwickelbaren Arzneimittel nicht direkt mit den für die genetischen Veränderung in die Zellen überführten Nukleinsäuren bzw. Genen verbunden ist. „Induced pluripotent stem cells“ sind Zellen, deren Eigenschaften mit denen humaner embryonaler Stammzellen vergleichbar sind, ohne dass embryonale Stammzellen zu ihrer Herstellung verwendet wurden. In den USA und in Japan werden solche Zellen als Gentherapeutika betrachtet. Durch die Einordnung dieser und anderer Nukleinsäure tragender Zellen, deren rekombinante Nukleinsäuren nicht direkt mit der therapeutischen Wirkung assoziiert sind, als somatische Zelltherapeutika ist jedoch sichergestellt, dass die Anforderungen an Arzneimittel für neuartige Therapien, hier die für somatische Zelltherapeutika und die für Gentherapeutika, angewendet werden können.

Nach der in Nr. 2.2.1 vorgeschlagenen Definition werden als Gentherapie-Arzneimittel nicht nur in vivo angewendete Arzneimittel erfasst, sondern auch „ex vivo“ verwendete. Darunter versteht das Paul-Ehrlich-Institut in diesem Zusammenhang bei der Herstellung genetisch modifizierter Zellen außerhalb des menschlichen Körpers verwendete Nukleinsäuren bzw. Vektoren. Eine Ausdehnung des Arzneimittelbegriffs in der Definition der Gentherapie-Arzneimittel auf Stoffe, die nicht am oder im Körper, sondern ex vivo verwendet werden, dürfte Abgrenzungsprobleme aufwerfen und entspricht auch nicht dem, was üblicherweise sonst unter einem Arzneimittel verstanden wird. Die Erläuterungen „in vivo or ex vivo“ sollten gestrichen werden und die Definition der Gentherapie-Arzneimittel auf Arzneimittel beschränkt bleiben, die in vivo angewendet werden.

Aus Sicht des Paul-Ehrlich-Instituts wäre es auch wünschenswert, das frühere Kapitel 4 („SPECIFIC STATEMENT ON XENO-TRANSPLANTATION MEDICINAL PRODUCTS“) beizubehalten und hier die Anforderungen an xenogene somatische Zelltherapeutika und Xenotransplantate zusammenzufassen.

Eine detaillierte Stellungnahme des Paul-Ehrlich-Instituts ist beigefügt (Anlage 2). Der darin enthaltene Vorschlag einer modifizierten Definition der Gentherapeutika und einer entsprechenden Anpassung der Definition der somatischen Zelltherapeutika berücksichtigt die Ergebnisse der Diskussionen in den fachlich einschlägigen Arbeitsgruppen der Europäischen Arzneimittelagentur.

Mit freundlichen Grüßen

Prof. Dr. Klaus Cichutek
Vizepräsident

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.1 **Introduction** 3rd paragraph	« In principle, all relevant guidelines developed by the European Medicines Agency (EMEA) or the International Conference on Harmonisation (ICH) should be followed. Any exception and/or deviation shall be appropriately justified in Module 2.” **Comment** As general quality requirements/characteristics of these products are included in the Ph. Eur. the reference to the Eurepoean Pharmacopoeia seems appropriate.	
5th paragraph	“The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells, the ability to proliferate, to differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the integration of nucleic acids sequences or genes into the genome, their long time functionality or oncogenicity and the mode of use. **Comment:** Several relevant “risk aspects” for cell-based products according to the draft guideline on human cell-based products might be included.	“The risk analysis may cover the entire development. Risk factors include but are not limited to: the origin of the cells (e.g., autologous or allogeneic), the ability to proliferate, to differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the mode of administration , the duration of exposure, the nature of the gene therapy medicinal products, the integration of nucleic acids sequences or genes into the genome, their long time functionality or oncogenicity and the mode of use.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.2 Definitions 2.2.1 Gene therapy medicinal product	*" 2.2.1. Gene therapy medicinal product* means a medicinal product: - that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and - whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence."	*Gene therapy medicinal product* means a medicinal product: the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used in or administered to human beings with a view to regulating, repairing, replacing, adding, mutating or deleting a genetic sequence and/or where the recombinant nucleic acid is an added, mutated or deleted genetic sequence; and whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid or to cells harbouring a nucleic acid which has these properties.
2.2.2. Somatic cell therapy medicinal product	*"2.2.2. Somatic cell therapy medicinal product* means a medicinal product that: - contains or consists of engineered cells or tissues within the meaning of Article 2(1)(c) of Regulation 1394/2007/EC, and - is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues." **Comment**: See above	*Somatic cell therapy medicinal product* means a medicinal product that: - contains or consists of cells or tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties have been altered, and - is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues. The manipulations listed in Annex I to Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations."

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.3 Modul 3 (Quality) 2.3.2 Specific requirements for gene therapy medicinal products 5 (a) iii)	" (iii) In the case of genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, *i.e.* the vector and the human or animal cells. The principles of Good Manufacturing Practice shall apply from the bank system used to produce the vector onwards."	(iii) In the case of genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, *i.e.* the starting materials to produce the vector and the human or animal cells. The principles of Good Manufacturing Practice shall apply from the bank system used to produce the vector onwards."
2.3.2 Specific requirements for gene <u>therapy medicinal products</u> 5 (e)	"(e) For plasmids quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product." **Comment:** Issue of 5(e) has more character of a guideline and may not have to be outlined in detail in the annex.	Delete.
5 (f)	*"(f) For genetically modified cells the phenotypic characteristics of the cells pre- and post-transduction shall be tested, before and after any subsequent freezing/storage procedures*". **Comment:** "Phenotype characteristics" is not appropriately defined (eg cell surface markers and/or transgene expression). Therefore, we propose to delete "phenotypic".	"(f) For genetically modified cells the relevant ~~phenotypic~~ characteristics of the cells pre- and post-transduction shall be tested, before and after any subsequent freezing/storage procedures".

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	**4.** For certain somatic cell therapy medicinal products and tissue engineered products, ( ) the active substance and the finished product can be closely related or nearly identical. In those cases, only relevant sections and items need to be completed, if justified **Comment:** ( ) "Starting material" has been deleted compared to a similar sentence in the draft guideline on human cell-based products.	**4.** For certain somatic cell therapy medicinal products and tissue engineered products, the starting material, the active substance and the finished product can be closely related or nearly identical. In those cases, only relevant sections and items need to be completed, if justified
6 (a) Starting material (i)	**"**(i) Information on donation, procurement and testing shall be provided…." **Comment:** The subject of the testing should be named.	"(i) Information on donation, procurement and testing of cells/ tissues used as starting material shall be provided…."
(ii)	(iii) The potential variability introduced through the starting material (*e.g.*, variability of donor population such as age, characteristics of cells) shall be addressed insofar as manufacturing process, validation, characterisation, control, stability are concerned, both for the active substance and the finished product. **Comment:** The wording should be clearified. **.** Procedures for selection of appropriate donor material are not mentioned.	(iii) The influence of the potential variability of cells/tissues used as starting material (*e.g.*variability of donor population such as age, characteristics of cells) on the manufacturing process, validation, characterisation, control, stability should be addressed both for the active substance and the finished product.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
(iv)	(iv) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents and suitability of the animal facilities shall be provided.	(iv) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents <u>including vertically transmitted micro-organisms</u> and viruses and evidence for the suitability of the animal facilities shall be provided.
(v)	(v) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of transgenic animal shall be provided.	(v) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of transgenic <u>and/or knock-out</u> animal shall be provided.
(b) Manufacturing process: (i)	(i) All steps of the manufacturing process starting from the receipt of the organs/tissue/cells up to the formulation and filling of the finished product shall be described. **Comment:** Although donation and transport of cells/tissues are covered by Dir. 2004/23/EC, this shall be described since procurement is a critical step (eg microbiologic safety)	(i) All steps of the manufacturing process starting from the receipt of the organs/tissue/cells up to the formulation and filling of the finished product shall be described. Donation, procurement and transport of cells/tissues as starting material shall be described since procurement is considered to be a critical step (e.g. for microbiological control of the product).
(iii)	(iii) The manufacturing process should be validated to ensure batch consistency, functional integrity of the cells at the moment of application/ administration, the proper differentiation state and the cell function with additional substances throughout the manufacture. If cells are grown	(iii) The manufacturing process should be validated to ensure batch consistency, proper differentiation state, cell function and functional integrity of cells at the moment of application/administration,. ~~the proper differentiation state and the cell function with additional substances throughout the manufacture.~~

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
	directly inside or on a matrix, scaffold or device, information on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination shall be provided. **Comment:** The wording is unclear	If cells are grown directly inside or on a matrix, scaffold or device, information on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination product shall be provided.
2.3.3 (f) Reference materials	"(f) Reference materials (i) A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised, unless justified." **Comment:** The term "Reference standard" in this context should be clarified as this term is usually used for authorised Pharmacopoe-standards. This might be hard to achieve for the respective products as mostly in house standards will be used.	
2.4 Module 4 (Non-clinical data) 2.4.1. General requirements for <u>advanced therapy medicinal products</u> 3.	**3.** The safety, suitability and biocompatibility of any additional substances such as … **biomaterials…** **Comment:** This requirement may produce some practical problems as the safety documentation of the mentioned products produced by other companies may not be available for the applicant for reasons of confidentiality.	Delete.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.4.2. Specific requirements for gene therapy medicinal products	**Comment:** There is no consistency between Modules 4 and 5 concerning structure and wording.	Adapt according to comment.
1. Pharmacokinetics (b)	"(a) Biodistribution studies, shall include investigations on persistence, clearance and mobilisation. Biodistribution studies should especially address the risk of germ line transmission. (b) Investigations of shedding of transmissible vector, micro-organism or virus and risk of transmission to third parties shall be provided with the environmental risk assessment where appropriate." **Comment**: 1) These two parts should be harmonised with the corresponding parts in Modul 5. 2) The wording "transmissible vector" is misleading. Shedding studies and assessment of the riks of horizontal transmission and its consequences are to be performed for any type of viral vector/virus which can transduce cells or infect humans or animals.	(b) Investigations of shedding of ~~transmissible~~ transducing vector, infectious micro-organism or virus and risk of transmission to third parties shall be provided with the environmental risk assessment where appropriate."

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
(c)	(c) Repeated dose toxicity studies …..The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. **Comment:** 1) Justification for the duration of the studies should be provided.	(c) Repeated dose toxicity studies…. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration should be provided.
(f)	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, where appropriate according to relevant guidelines. **Comment:** The requirement for generally studying effects on fertility and general reproductive function is stringent but may not be necessary for, e.g., genetically modified cells administered to the brain.	(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, where appropriate and according to relevant guidelines, unless otherwise justified.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products	**Comment:** There is no consistency between Modules 4 and 5 concerning structure and wording.	
1. Pharmacology	(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied. **Comment:** The interaction of cells and surrounding tissue may be difficult to study in some cases.	(a) The primary pharmacological studies should be adequate to demonstrate the proof of principle. The desired interaction of the applied cells with the non-cellular structural component(s) of the product and the interaction of the cell-based products with the surrounding tissue should be studied unless otherwise justified.
3. Toxicology		
(b)	(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product. **Comment:** See comment (b) under 2.4.2 .Justification for the duration of the studies should be provided.	(b) The duration of observations may be longer than in standard toxicity studies, depending on the lifespan of the medicinal product. A justification of the duration should be provided.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
(c)	(c) Conventional carcinogenicity and genotoxicity studies are normally not required. However, the tumourigenic potential of the product shall be studied unless otherwise justified.	(c) Conventional carcinogenicity and genotoxicity studies are normally not required. However, the tumourigenic potential of the product shall be studied unless otherwise justified.
(e)	(e) In case of cell-based products containing animal cells, the associated specific safety concerns such as virus reactivation shall be addressed. **Comment:** Instead of the virus reactivation the main safety concern should be pointed out. This is transmission of xenogeneic pathogens humans	(e) In case of cell-based products containing animal cells, the associated specific safety concerns such <u>as ~~virus reactivation~~ xenogeneic pathogens which may be transmitted to humans</u> shall be addressed.
2.5 Module 5 (Clinical data)	**General comments:** See comments 1), 3) 4) under general comments. There is no consistency between Modul 4 and 5 concerning structure and wording,. There should be consistency between sections egarding pharmacology-pharmacodynamics, pharmacokinetics. The assessment of “efficacy”.is not addressed. In the “general requirements” there is only a statement in relation to combined products and in relation to long term efficacy follow-up, and a weak statement that “proposed indications …supported by clinical studies….	Adapt.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.1. General requirements for advanced therapy medicinal products	**"1.** In general, the requirements for Module 5, as described in Part I of the Annex shall apply. Deviations from Module 5 and from applicable existing guidelines shall be justified in Module 2." **Comment:** For clinical data deviations from the applicable existing guidelines should only be acceptable if appropriately scientifically justified.	**1.** In general, the requirements for Module 5, as described in Part I of the Annex shall apply. Any deviations from Module 5 and from applicable existing guidelines shall be scientifically justified in Module 2.
4./5.	**4.** Dose selection and schedule … **Comment:** The sequence of bullet points should be changed. Bullet point 5 should be point 4, and 4 should be 5 and followed by point 6.	
6.	**6.** Proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions evidence of long term efficacy may be required. The strategy to evaluate long term efficacy should be provided. **Comment:** It should be clarified that long term efficacy data are not suitable to replace efficacy data at the time of marketing authorisation.	**6.** ~~Proposed indications~~ The efficacy in proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions evidence of long term efficacy may be required. The strategy to evaluate long term efficacy should be provided.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.2. Specific requirements for gene therapy medicinal products 2.5.3. Specific requirements for somatic cell therapy medicinal product 2.5.4. Specific requirements for tissue engineered products	There is no consistency in structure and requirements between the sections and with the corresponding sections of Module 4 (non-clinical data) .	
2.5.2. Specific requirements for gene therapy medicinal products 3.	**3.** Safety studies shall address aspects such as: - emergence of replication competent vector; - emergence of new strains; - reassortment of existing genomic sequences; - neoplastic proliferation due to insertional mutagenicity **Comment:** Safety studies for gene therapy MPs. Immune system monitoring is considered important	**3.** Safety studies shall address aspects such as: - emergence of replication competent vector; - emergence of new strains; - reassortment of existing genomic sequences; - neoplastic proliferation due to insertional mutagenicity - immune system monitoring and immune response against all components of the gene therapy medicinal product.

SPECIFIC COMMENTS ON TEXT		
Proposal to amend Annex I to Directive 2001/83/EC		
Chapter/ paragraph no.	**Comment and rationale**	**Proposed change (if applicable)**
2.5.3. Specific requirements for somatic cell therapy medicinal product	**1.** For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules shall be addressed. **Comment**: These requirements are relevant for both somatic cell therapy and tissue engineered products and should be addressed in both sections. However the requirement itself to address the PK profile of biomolecules is too stringent and can often only be addressed in preclinical studies.	**1.** For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of these molecules should be addressed, if feasible.
	Comment: Requirements specific for xenogeneic somatic cell therapy medicinal products and xenotransplants should be summarized in a separate chapter.	

Comment of the Paul-Ehrlich–Institut (PEI)
on the Proposal to amend Annex I to Directive 2001/83/EC regarding the definition of gene therapy and somatic cell therapy medicinal product
Public Consultation Paper No.2008-04-08

The definitions of gene therapy medicinal products (GTMP) and of somatic cell therapy medicinal products (SCT MP) are of eminent importance referring to the scope of the Regulation (EC) No 1394/2007. The proposals for updated definitions of gene therapy and somatic cell therapy medicinal products are suggested being slightly modified.

A. Proposal to optimize the proposed gene therapy medicinal product definition (GTMP)

Summary of issues posed by the proposed GTMP definition

The Paul-Ehrlich-Institut would like to bring to the attention of the EC that the proposed definition for gene therapy medicinal product (GTMP) poses major issues.

- A literally exact interpretation of the definition proposed by the EC (medicinal product is the active substance (DNA, vector, genetically modified cell, virus or microbe in, e.g., buffer or another formulation) leads to the conclusion that many GTMPs presently under investigation will be excluded (e.g., all viral vectors including those currently tested for vaccination/ immunotherapy, cardiovascular disease, hemophilia and other diseases, genetically modified cells including those tested to treat X-SCID and ADA-SCID, tumor vaccines) and another GTMP already proposed for market authorisation (Cerepro, a GTMP consisting of a replication-incompetent adenoviral delivery vector transferring the thymidine kinase gene of Herpes simplex virus (HSV-tk) into cancer cells in vivo). These products either contain added genes (in the genetically modified cells administered to patients) or they are all designed to <u>add</u> a genetic sequence to cells in vivo (viral vectors). In these cases, the added genes do not regulate, repair or replace a targeted genetic sequence.
- It is acknowleged, however, that there are MPs which add genes intended to regulate, repair or replace a targeted genetic sequence and we suggest including these MPs in the new GTMP definition. Future therapies may also involve the deletion and mutation of genetic sequences. After all, gene repair was the initial theoretical intention in gene therapy which will become a practicle possibility in the foreseeable future.
- The definition proposed by the EC may also include “conventional” live attenuated vaccines (encompassing an added gene or not) as well as live vector vaccines used to prevent infectious disease. These vaccines are sometimes termed “genetic vaccines”. The definition proposed by the EC also includes DNA/nucleic acid vaccines. The quality, safety and efficacy considerations used for GTMPs should also apply to these prophylactic vaccines against infectious diseases. If they were formally excluded from the definition, PEI proposes including such an obligation elsewhere in Annex I to Directive 2001/83/EC and to name these products “genetic vaccines”.

Listed below are the GTMP definition proposed by the EC followed by a modified definition proposed by the PEI which is aimed at solving the issues raised above. Although the definition may look complex, it has the advantage of describing rather exactly the products included in the novel GTMP definition. The GTMP definition suggested by the Paul-Ehrlich-Institut also takes into consideration current gene therapy developments in science, which may only in the midterm future lead to GTMP developments for clinical use. The Paul-Ehrlich-Institut prefers an exact, although complex definition over a general descriptive and less exact definition which would have to be explained by additional papers.

GTMP definition suggested by the Paul-Ehrlich-Institut (termed GTMP definition suggested by PEI in this paper)

Gene therapy medicinal product

means a medicinal product:

- the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used in or administered to human beings with a view to regulating, repairing, replacing, adding, mutating or deleting a genetic sequence and/or where the recombinant nucleic acid is an added, mutated or deleted genetic sequence; and
- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid or to cells harbouring a nucleic acid which has these properties. .

GTMP definition proposed by the EC in the Public Consultation Paper No. 2008-04-08 of 8 April 2008
(termed definition proposed by the EC in this paper)

Gene therapy medicinal product

means a medicinal product:

- that contains or consists of a nucleic acid sequence used in or administered to human beings, *in vivo* or *ex vivo*, with a view to regulating, repairing or replacing a targeted genetic sequence; and
- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Reflections on the proposed GTMP definition

According to the perception of the Paul-Ehrlich-Institut the GTMP definition proposed by the EC includes the following products:
- any of the substances listed above, only if used “with a view to regulating, repairing or replacing a targeted genetic sequence” and “whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid (sequence) it contains, or to the product of genetic expression of this sequence”;
- siRNA, shRNA and other RNAs, if produced by biological methods or if contained in or produced by using biological starting material (e.g., PCR, cell-cell fusion, MIDGE DNA);
- plasmid DNA used in vivo (which is produced by biological methods);
- non-viral vectors containing plasmid DNA or biologically produced nucleic acids;
- linear single or double-stranded DNA and biologically produced oligonucleotides.

However, the proposed definition as of 08 April 2008 may exclude the following products:
- chemically synthesized RNA or DNA;
- RNA, oligonucleotides and plasmid DNA, if these substances or the products made in or by the cells from these substances are not intended to exert a therapeutic, prophylactic or diagnostic effect;
- RNA, oligonucleotides and plasmid DNA, if these substances are not administered “with a view to regulating, repairing or replacing a targeted genetic sequence”.

The Paul-Ehrlich-Institut would like to suggest changing the GTMP definition to reflect the following considerations:

1) The Paul-Ehrlich-Institut suggests including the following products in the GTMP definition:
- all replication-incompetent viral vectors (which all contain plasmid DNA or biological nucleic acids);

- all replication-competent vectors, which are recombinant micro-organisms and viruses carrying a therapeutic, in vivo diagnostic or preventive nucleic acid or carrying recombinant mutant or non-mutant wildtype genes;
- all cells genetically modified with a therapeutic, in vivo diagnostic or preventive nucleic acid including genetically modified cells where the genetic modification has led to a deletion, mutation or addition of a genetic sequence for a therapeutic, in vivo diagnostic or preventive purpose.
Therefore, added nucleic acids or nucleic acids intended to mutate or delete existing nucleic acids (knock-out mutations) should also be included in the GTMP definition.

All replication-incompetent vectors and all replicating (oncolytic) viruses can be included in the GTMP definition by stating that GTMPs are medicinal products
"- the active substance of which contains or consists of a recombinant nucleic acid, where the recombinant nucleic acid is used with a view to regulating, repairing, replacing, adding or deleting a genetic sequence…". This phrasing still excludes genetically modified cells because their recombinant nucleic acids will not be used with a view to regulating, repairing, replacing, adding or deleting a genetic sequence. This intended process is already completed within the genetically modified cells before they are administered as the active substance of a GTMP to patients/subjects.

In order to include in the GTMP definition cells which have been genetically modified to result in their nucleic acids being an added, mutated or deleted genetic sequence, this has to be stated in the definition. It is therefore suggested stating that GTMP means a medicinal product "… - the active substance of which contains or consists of a recombinant nucleic acid, where… the recombinant nucleic acid is an added, mutated or deleted genetic sequence;…".

We propose using the term "recombinant" nucleic acid because all GTMPs are prepared by recombinant DNA technology. Using this wording will exclude only non-recombinant oncolytic viruses. For non-recombinant oncolytic viruses, the GTMP considerations should still apply. It is suggested stating this elsewhere in Annex I to Directive 2001/83/EC.

If the EC intends to exclude cells genetically modified for other than preventive, in vivo diagnostic or therapeutic purposes in the final version of the new GTMP definition, the technical requirements for GTMP as listed in the GTMP-part of the revised Annex I to Directive 2001/83/EC should also be used for the genetically modified cells, even if these cells will be somatic cell therapy and/or tissue engineered products.

2) By using the term "in vivo or ex vivo" in the GTMP definition proposed by the EC, it was possibly intended to include nucleic acids used on cells in culture, i.e. ex vivo, in the GTMP definition and to allow applicants to obtain marketing authorisation for ex vivo used vectors. Usually only substances and preparations made from substances intended to be applied on or in the body are classified as medicinal products. We suggest deleting the phrase "in vivo or ex vivo" from the definition.

3) The term "nucleic acid sequence" relates only to a property of a nucleic acid, namely its sequence, but not to the substance "nucleic acid". We therefore propose using the term "nucleic acid". Nucleic acid is always more than one nucleotide, it can also be single stranded or double stranded. Oligonucleotides will also be nucleic acids.

4) The exclusion of preventive vaccines against infectious diseases from the GTMP definition will allow applying established principles and requirements for preventive vaccines. These are prophylactic nucleic acid/DNA vaccines, prophylactic non-viral vector vaccines, prophylactic live vector vaccines, replicating recombinant attenuated viruses or microbes used as prophylactic vaccines and recombinant hybrid viruses (the genome of which is a combination of the genome

of two viruses). Technically, the only possibility the Paul-Ehrlich-Institut has found to exclude such prophylactic vaccines is to state this exclusion accurately in the GTMP definition (see third hyphen of the GTMP definition suggested by PEI).

The Paul-Ehrlich-Institut would like to recommend ensuring that suitable gene therapy requirements in Annex I to Directive 2001/83/EC and in guidelines will also have to be met for these vaccines because some of the quality, safety, efficacy and environmental risk considerations of GTMP may apply to these vaccines, depending on a case-by-case evaluation.

5) By including after the second hyphen of the GTMP definition proposed by the EC, the wording "…- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid;…" it was probably intended to exclude from the GTMP definition cells genetically modified with genes/nucleic acids which do not contribue to the therapeutic, in vivo diagnostic or prophalyctic purpose of the treatment of humans. Examples may be long established human cell lines containing neo genes which had been used during the establishment for the selection of cell clones, which could then be tested for a wished characteristic or property. Another example for such genetically modified cells may be cells harbouring recombinant nucleic acid mediating expression of cell surface markers, which can be used for in vitro selection, or "induced pluripotent stem cells". One may refer to these cells "cells genetically modified for manufacturing purposes".

However, recent science shows that human embryonic stem cell-like cells can be produced from human somatic cells by transferring nucleic acids encompassing three crucial genes using a retroviral vector. These cells (termed induced pluripotent stem cells (iPS cells)) could be starting material for human somatic cell therapay medicinal products. For this, the iPS cells would be differentiated to other human cells, e.g., blood stem cells, and then administered to patients. Some of the safety issues which these cells pose are currently believed to directly relate to the nucleic acid transfer. When these cells are administered to patients, however, the therapeutic effect will not relate to the transferred nucleic acids or products of their expression. The Paul-Ehrlich-Institut suggests applying to iPS cells and cells genetically modified for manufacturing purposes both, the principles and requirements for GTMPs and somatic cell therapy medicinal products..

The Paul-Ehrlich-Institut would like to draw attention to the fact that all genetically modified cells (harbouring a therapeutic, in vivo diagnostic or preventive nucleic acid) would possibly be excluded form the GTMP definition, if the phrase after the second hyphen would only be "…- whose therapeutic, prophylactic or diagnostic effect relates directly to the nucleic acid it contains, or to the product of genetic expression of this nucleic acid ". The reason for this is that the active substance of cell-containing GTMPs are the genetically modified cells, but neither the cells without the contained recombinant nucleic acid alone nor the recombinant nucleic acid not being part of the cells. In this sense, the effect of the cell-containing GTMPs therefore relates to the genetically modified cells in their entirety, not to the contained recombinant nucleic acid only nor to the cells without this nucleic acid.

B. Proposal to optimise the proposed definition of somatic cell therapy medicinal product (SCT MP)

Reflections on the proposed SCT MP definition

The proposed SCT MP definition excludes cells intended for immunotherapy use (see below) and should therefore be slightly reworded. The intention of the EC is welcomed to clarify that

“substantial manipulation, so that biological characteristics, physiological functions or structural properties” of cells in SCT MP should be equivalent to the meaning of “engineering” in the tissues engineered product (TEP) definition is welcomed by the Paul-Ehrlich-Institut.

Article 2(1) (c) of Regulation (EC) No. 1394/2007 says:
“Cells or tissues shall be considered ‘engineered’ if they fulfil at least one of the following conditions:
— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,
— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.”
Therefore, although it was probably intended to refer to the first hyphen only in Article 2(1), the chosen wording in the proposed definition refers to both hyphens, which is unfortunate.

Taken together, the proposed SCT MP definition as of 08 April 2008 (see below) therefore says that a somatic cell therapy medicinal product is:
“a medicinal product that
- contains or consists of engineered cells or tissues that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved and
- is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
The manipulations listed in Annex I (to Regulation (EC) No. 1394/2007), in particular, shall not be considered as substantial manipulations.”

This text would exclude SCT MP which are intended for immunotherapy because only “biological characteristics, physiological functions or structural properties *relevant for the intended regeneration, repair or replacement*” are named. SCT MPs for immunotherapy are not intended for regeneration, repair or replacement. To include under the term “SCT MPs” all cell-containing products with non-homologous use is in line with the current understanding that tissue engineered products are a subgroup of SCT MPs, although there are a few tissue engineered products which are not SCT products.

It is also recognised that cells genetically modified by therapeutic, in vivo diagnostic or preventive nucleic acid(s) will falls under the definition of SCT-MP and GTMP or TEP and GTMP. In this case and according to Article 2 No. 5 to Regulation (EC) No. 1397/2007, these genetically modified cells should be considered GTMPs.

SCT MP definition proposed by the Paul-Ehrlich-Institut
Somatic cell therapy medicinal product
means a medicinal product that:
- contains or consists of cells or tissues <u>that have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties have been altered,</u> and
- is presented as having properties for, or is used in or administered to human beings with the view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.
<u>The manipulations listed in Annex I to Regulation (EC) No. 1394/2007, in particular, shall not be considered as substantial manipulations.</u>”

SCT MP definition proposed by the EC in the Public Consultation Paper No. 2008-04-08 of 8 April 2008

Somatic cell therapy medicinal product
means a medicinal product that:
- contains or consists of engineered cells or tissues within the meaning of Article 2(1)(c) of Regulation 1394/2007/EC, and
- is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

Tissue engineered product definition according to Article 2 of Regulation (EC) No. 1394/2007

Tissue engineered product'
means a product that:
— contains or consists of engineered cells or tissues, and
— is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:
— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations …